REMARKS

In the October 22, 2002 Office Action, the Examiner rejected claims 31, 33 and 40 pending in the application. This Response adds new claims 48 through 50 for consideration. After entry of the foregoing amendments, claims 31, 33, 40, and 48-50 (two independent claims; six total claims) remain pending in the application. Reconsideration is respectfully requested.

Claims 31, 33 and 40 stand rejected under 35 U.S.C. §102(b) as being anticipated by either Gaskell and Brownsey (Clin. Chem., 29(4): 677-680, 1983), Gaskell (Steroids, 55: 458-462, 1990), Bonfanti (Cancer Research, 50: 68706875, 1990) or Davoli (Anal. Chem., 65: 2679-2685, 1993). Applicants respectfully traverse this rejection.

In particular, with respect to the Gaskell and Brownsey reference, the Examiner states that Gaskell and Brownsey teach a method for quantifying estradiol-17β, where a deuterated estradiol internal standard is added to a plasma sample, mixing a solid-phase coupled antiserum specific for both the labeled and unlabeled estradiol, and then drying and analyzing the extract using gas chromatography (GC)-mass spectrometry (MS). The Examiner further states that the ratios of the estradiol to deuterated estradiol are compared to a standard curve for quantification.

The Gaskell and Brownsey reference describes an alternative approach for establishing fractionation procedures that complement the specificity of GC-MS detection. In particular, the Gaskell and Brownsey reference states that "Extraction of estradiol-17β from plasma by using a solid-phase-coupled antiserum rapidly and specifically fractionates samples before the GC-MS procedure." The reference also states that a deuterium-labeled internal standard is used to enhance precision. (See page 677 of the reference). Applicants contend that this reference paper specifically teaches away from the application by requiring a derivatization step after affinity capture to prepare for GC-MS. (See page 678 of the reference where a description of sample preparation includes plasma extraction, determination of extraction efficiency, and derivatization procedure). Moreover, the Gaskell and Brownsey reference further teaches away from Applicants' invention by requiring an additional chromatographic step between affinity capture and mass spectrometry. The additional chromatography step utilized in Gaskell and Brownsey has the potential to introduce errors in the analysis by shifting retention times of the analyte and its deuterated isoform. Finally, unlike Applicants' claimed method, the Gaskell and Brownsey reference fails to monitor the ion signals from both the analyte and the IRS in the same mass

spectrum. Instead, a peak-switching approach is used which selectively monitors only the analyte or the IRS while the eluate from the chromatographic column.

With respect to the 1990 Gaskell reference, the Examiner states that Gaskell teaches a method for quantifying DHA-S, where a deuterated DHA-S internal standard is added to a serum sample and then added to an immunoaffinity column. The Examiner further states that the immunoaffinity eluate is analyzed by gas-chromatography-mass spectrometry and that the ratios of the DHA-S and deuterated internal standard are compared to a standard curve for quantification.

The 1990 Gaskell reference discloses quantification of DHA-S in serum using fast atom bombardment (FAB)/tandem mass spectrometry. The quantification method includes: (1) stable isotope dilution using an internal standard, (2) isolation of the analyte by immunoadsorption, namely highly selective retention on a solid phase incorporating bound antiserum raised against a conjugate of DHA, and (3) detection of both analyte and internal standard during limited mass range parent ion scanning during tandem MS. (See page 460 of the reference). Accordingly, unlike the Examiner's assertion on page 3 of her office action, the Gaskell reference utilizes FAB/MS instead of GC-MS.

Nevertheless, the 1990 Gaskell reference also teaches away from Applicants' claimed invention by using tandem MS for quantification. In other words, different mass spectrometric measurements are taken of similar portions of the same serum extract and compared. (See page 461 of the reference). Unlike Applicants' claimed invention, the analyte and IRS are not measured using MS in a single measurement. In addition, the 1990 Gaskell reference also teaches away from Applicants' claimed invention by requiring multiple sample preparation steps in between extraction and mass spectrometry. (See pages 460-461 of the reference).

With respect to the Bonfanti reference, the Examiner contends that Bonfanti teaches a method for quantifying O^6-butylguanine where a deuterated internal standard is added to a serum sample and then loaded onto an immunoaffinity column. The Examiner then states that the immunoaffinity column eluate is analyzed by GC-MS and that the ratios of the O^6-butylguanine and deuterated internal standard are compared to a standard curve for quantification.

The Bonfanti reference essentially uses the same approach as the Gaskell and Brownsey reference previously discussed above. More specifically, the Bonfanti reference uses a

methological approach that involves different separation factors that include: "binding to an antibody, separation by high resolution gas chromatography, and detection of a specific ion in the mass spectrometer." Moreover, this reference specifically states that "the first separation factor is very important and has to be efficient, since high resolution gas chromatography-mass spectrometry has the serious drawback of requiring thorough purification procedures before sophisticated analysis. . . . The selectivity of the purification step by immunoaffinity chromatography depends on the specificity of the antibody employed." (See page 6872 of the reference).

Like the Gaskell and Brownsey reference, the Bonfanti reference teaches away from Applicants' claimed invention by requiring an additional chromatographic step between affinity capture and mass spectrometry. As previously stated, this additional chromatography step has the potential to introduce errors in the analysis by shifting retention times of the analyte and its deuterated isoform. Moreover, the Bonfanti reference fails to monitor both the analyte and the IRS in the same measurement using MS.

Finally, with respect to the Davoli reference, the Examiner contends that Davoli teaches a method for quantifying diethylstilbestrol where deuterated internal standards are added to urine samples that are loaded onto immunoaffinity columns. The Examiner further states that the eluate is analyzed by fast atom bombardment mass spectrometry and that quantification is made by comparison to a standard curve.

In the Davoli reference, extraction was done by injecting samples directly into an immunoaffinity column containing antidiethylstilbestrol antibodies bound to a Sepharose matrix, and analysis was done by on-line high-performance liquid chromatography with ultraviolet and continuous-flow fast atom bombardment mass spectrometry detectors. (See page 2681 of the reference). Once again, this reference also teaches away from Applicants' claimed invention by requiring additional steps, namely high-performance liquid chromatography and fast atom bombardment in addition to MS. Once again, these additional steps create the possibility of introducing errors in the analysis. Moreover, unlike Applicants' claimed invention, Davoli selectively monitors only the analyte or the IRS when obtaining measurements. In Applicants' claimed invention, both the analyte and the IRS signal are measured in a single measurement.

Applicants' claimed invention overcomes potential problems in all of the prior art cited by the Examiner by measuring both the analyte and the IRS signal in a single measurement.

Essentially, in Applicants' claimed invention, the mass spectrometry accomplishes both the separation and the mass measurement in a single step.

In view of the foregoing, Applicants respectfully submit that all of the pending claims fully comply with 35 U.S.C. §112 and are allowable over the prior art of record. Reconsideration of the application and allowance of all pending claims is earnestly solicited. Should the Examiner wish to discuss any of the above in greater detail or deem that further amendments should be made to improve the form of the claims, then the Examiner is invited to telephone the undersigned at the Examiner's convenience.

Respectfully submitted,

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